General

Guideline Title

Plerixafor for autologous hematopoietic stem cell mobilization and transplantation for patients in Ontario.

Bibliographic Source(s)

Kouroukis CT, Varela NP, Bredeson C, Kuruvilla J, Xenocostas A, Stem Cell Transplant Steering Committee. Plerixafor for autologous hematopoietic stem cell mobilization and transplantation for patients in Ontario. Toronto (ON): Cancer Care Ontario (CCO); 2015 Sep 15. 45 p. (Evidence-based series; no. SCT-7). [33 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario (CCO) Web site for details on any new evidence that has emerged and implications to the guidelines

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Recommendation 1

Adding plerixafor to granulocyte colony-stimulating factor (G-CSF) is an option for initial mobilization for patients with non-Hodgkin lymphoma or multiple myeloma who are eligible for autologous stem cell transplantation (SCT) when chemotherapy cannot be used and only G-CSF mobilization is available.

Recommendation 2

For patients with low peripheral blood $CD34^{+}$ cells counts (e.g., <10/uL) at the time of anticipated stem cell harvesting, or with an inadequate first-day apheresis collection, it is recommended that plerixafor be added to the mobilization regimen to maximize stem cell collection and to prevent the need for remobilization.

Recommendation 3

For patients who have failed a previous mobilization attempt, it is recommended that they undergo remobilization with G-CSF and plerixafor, with

or without chemotherapy.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Any disease or condition requiring autologous hematopoietic stem cell transplantation (SCT), including non-Hodgkin and Hodgkin lymphoma, multiple myeloma, and germ cell tumours

Guideline Category

Treatment

Clinical Specialty

Hematology

Internal Medicine

Oncology

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To summarize the available data regarding the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection before autologous stem cell transplantation (SCT) and to provide recommendations on its use

Target Population

All adult patients considered for autologous stem cell transplantation (SCT) and meeting one of the following criteria:

- Have not been mobilized before (i.e., the case of up front mobilization in naïve patients who may or may not be at risk of being poor mobilizers)
- Are failing initial mobilization (based on peripheral blood $CD34^+$ cells count before first day of apheresis, or the total number of $CD34^+$ cells collected on the first day of apheresis)
- Have failed a prior mobilization attempt (i.e., are poor mobilizers)

Interventions and Practices Considered

Plerixafor in combination with granulocyte colony-stimulating factor (G-CSF) for stem cell mobilization before autologous transplantation

Major Outcomes Considered

- Total number of $CD34^+$ cells collected during apheresis
- Number of apheresis procedures
- Peripheral blood $CD34^+$ cells counts
- Proportion of patients who proceed to autologous stem cell transplantation (SCT)
- Survival rate (post-SCT and in untransplanted patients)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation, using the ADAPTE framework, or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this document, the following sources were searched for existing guidelines that addressed the research questions:

- Practice Guideline Databases:
  - the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), and
  - the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse (NGC)
- Electronic Databases: MEDLINE and EMBASE

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. Two guidelines were identified as potentially relevant and considered for full text review and quality assessment using the AGREE II instrument. However, the reporting quality was low, taking into consideration the methods used to search for the evidence, the methods used to formulate the recommendations, and the criteria for selecting the evidence. In addition stakeholder involvement, among other domains needed for undergoing quality assurance, was not reported. For these reasons, the recommendations made in these two guidelines were not considered for endorsement or adaptation and no quality assessment was conducted.

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature.

Search for Existing Systematic Reviews

The Cochrane Database of Systematic Reviews was searched from January 2009 to April 2014 using the word "plerixafor". Systematic reviews older than six years were considered not relevant, because the main goal of a search for systematic reviews is to identify recent secondary sources covering the primary literature that may be helpful in the development of these recommendations.

Systematic reviews were included if:

1. The existing systematic review searched for studies evaluating the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection in adult or pediatric patients considered for autologous stem cell transplantation (SCT)
2. The literature search strategy for the existing review was reproducible and appropriate
3. The existing systematic review reported the sources searched as well as the dates that were searched

Identified systematic reviews that met the eligibility criteria would be assessed using the Assessing Methodological Quality of Systematic Reviews (AMSTAR) tool (a measurement tool to assess the methodological quality of systematic reviews) to determine whether or not an existing review could be incorporated as part of the evidentiary base. Any identified reviews that did not meet the criteria above, whose AMSTAR assessments indicated important deficiencies in quality, or that were otherwise not incorporated as part of the evidence base would be reported in the reference list, but not further described or discussed.

Search for Primary Literature

Literature Search Strategy

The MEDLINE (Ovid) (1996 through April 18, 2014) and EMBASE (Ovid) (1996 through Week 16, 2014) databases were searched for evidence in April 2014 and updated in March 2015. The search strategy included a logical combination of terms for the condition (stem cell transplantation), the intervention (plerixafor), and studies of interest (systematic reviews, clinical trials, nonrandomized studies with an appropriate control group). The full literature strategy used to retrieve potential relevant studies is presented in Appendix 1 of the original guideline document.

Study Selection Criteria and Protocol

Inclusion Criteria

Articles identified in this literature search were eligible for inclusion if they met the following criteria:

1. Primary studies evaluating the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection before autologous SCT
2. Published full-report articles of randomized control trials and nonrandomized studies with an appropriate contemporaneous control group
3. Studies reporting the outcomes of interest such as number of $CD34^{+}$ cells collected, number of apheresis procedures, proportion of patients who proceed to autologous SCT, and survival rate post-SCT

Exclusion Criteria

Studies were excluded if they were:

1. Abstracts, letters, case reports, comments, books, notes, or editorial-type publications
2. Because resources were not available for translation services, articles published in a language other than English

A review of the titles and abstracts that resulted from the search was conducted by one reviewer, and the reference list from these sources was searched for additional trials. For those items that warranted full text review, the same reviewer assessed each item independently.

Results

Search for Existing Systematic Reviews

The Cochrane Collaboration released a systematic review protocol in 2013 to evaluate the efficacy and safety of plerixafor for the mobilization of hematopoietic stem cells in people with non-Hodgkin lymphoma, Hodgkin lymphoma, or multiple myeloma and with the indication for autologous transplantation, but a full report has not been published yet. No other relevant systematic reviews were identified.

Systematic Review of the Primary Literature

Literature Search Results

While reviewing the primary literature few studies were identified that met the initial inclusion criteria, and therefore a post hoc subset of nonrandomized studies with historical groups was included, because these types of studies would help to inform the recommendations. Similarly, due to the shortage of comparative studies assessing the efficacy of plerixafor in both patients failing mobilization prior to autologous SCT, and patients who have failed a prior mobilization regimen, the inclusion criteria for this population was expanded to include single-arm studies with a sample size of at least 30 participants.

As presented in Figure 1 of the original guideline document, out of 2576 titles and abstracts identified in the search of the MEDLINE and EMBASE databases, 2302 appeared potentially eligible on initial review, and 160 of these were verified to be eligible for full text review. Eight additional studies were included for full text review based on the updated search in 2015. From these, 22 full-report studies were identified that evaluated the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection before autologous SCT, and reported the outcome of interest. The remaining 146 studies were excluded because they failed to pass the inclusion criteria.

Number of Source Documents

Search for Existing Systematic Reviews

No relevant systematic reviews were identified.

Search for Primary Literature

Twenty-two full-report studies met the inclusion criteria.

See Figure 1 in the original guideline document for a flow diagram depicting the study selection process.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction

Data extraction was conducted by one reviewer. All extracted data and information was assessed by a second reviewer, and audited by an independent auditor to verify the accuracy of the information obtained from the studies included in this report. For primary studies, key characteristics, including author, year of publication, study design, sample size, treatment arms, plerixafor indication/diagnosis, intervention and mobilization regimen, and years of data collection were extracted. Outcomes of interest including number of $CD34^+$ cells collected, number of apheresis procedures, proportion of patients who proceed to autologous stem cell transplantation (SCT), survival rate post SCT, and survival rate in untransplanted patients were extracted when available.

Assessment of Study Quality

For systematic reviews that would be used as the sole evidence base for the recommendations, the Assessing Methodological Quality of Systematic Reviews (AMSTAR) tool (a measurement tool to assess the methodological quality of systematic reviews) would be used to assess quality. For clinical practice guidelines (CPGs), the Appraisal of Guidelines Research & Evaluation (AGREE) II instrument would be used to assess quality. However, because of the time and effort necessary to properly implement the AGREE II instrument, it would be used only if adaptation of the recommendations was considered feasible by the members of the Working Group given the nature and coverage of the guideline and an informal assessment of the guideline's methods. Where recommendations from CPGs were not adapted, the evidence base in those CPGs would be informally assessed for completeness, and any relevant evidence within would be considered as a basis for recommendations in this report. Any meta-analysis would be assessed for quality using similar criteria as used for randomized controlled trials (RCTs), where appropriate. RCTs would be assessed for quality by examining the following seven criteria: method of randomization, reporting of blinding, power and sample size calculation, length of follow-up, reporting details of the statistical analysis, reporting on withdrawals to treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, nonrandomized, and single-arm evidence would be assessed according to full reporting of the patient selection criteria, the interventions each patient received, all relevant outcomes, and the source of funding. All authors reviewed and discussed a draft of this report with the aim of assessing the quality of the evidence as a whole, without the use of a scoring system or cut-offs, according to the policy of the Program in Evidence-Based Care (PEBC).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Recommendation Report Developers

This recommendation report was developed by a Working Group consisting of four haematologists/oncologists and a health research methodologist at the request of the Stem Cell Transplant Committee.

The Working Group was responsible for reviewing the evidence base, drafting the recommendations and responding to comments received during the document review process.

Recommendation Report Development Methods

The Program in Evidence-Based Care (PEBC) produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle. For Recommendation Reports this process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by a methodology experts and final approval by the Sponsoring Committee.

The PEBC uses the Appraisal of Guidelines Research & Evaluation (AGREE) II framework as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

Research Questions

The following research questions were developed to direct the search for available evidence to inform recommendations:

- Does the administration of plerixafor in combination with granulocyte colony-stimulating factor (G-CSF) for stem cell mobilization before autologous transplantation improve the outcome of patients who have not been mobilized before, when compared with G-CSF for stem cell mobilization alone or in combination with chemotherapy?
- Does the administration of plerixafor in combination with G-CSF for stem cell mobilization before autologous transplantation improve the outcome of patients failing mobilization when compared with G-CSF for stem cell mobilization alone or in combination with chemotherapy?
- Does the administration of plerixafor in combination with G-CSF for stem cell mobilization before autologous transplantation improve the outcome of patients who have failed a prior mobilization regimen when compared with G-CSF for stem cell mobilization alone or in combination with chemotherapy?

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Evidence on the cost-effectiveness of plerixafor was not considered in this report.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Recommendation Report Review and Approval

Internal Review

The recommendation report was reviewed by the Director of the Program in Evidence-Based Care (PEBC). The Working Group is responsible for ensuring the necessary changes are made. If those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

Report Approval by the Stem Cell Transplant Steering Committee

After internal review, the report was presented to the Cancer Care Ontario-Stem Cell Transplant Steering Committee (CCO-SCT). Members of the CCO-SCT reviewed the report, and formally approved the document during a meeting held on Thursday, September 10th, 2015.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by randomized controlled trials (RCTs), non-randomized controlled trials, retrospective cohorts, and single arm trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The use of plerixafor plus granulocyte colony-stimulating factor (G-CSF) "on demand" for those patients who appear to be mobilizing poorly was felt to be a useful strategy to maximize the benefits of plerixafor, minimize the risk of requiring remobilization, and therefore allow patients to proceed to transplant in a timely fashion. With many health-care centres opting to use plerixafor plus G-CSF "on demand" in poor mobilizers, the number of patients requiring remobilization is expected to decrease over time.

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario (CCO) makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.
- See the original guideline document for qualifying statements related to each specific recommendation.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Kouroukis CT, Varela NP, Bredeson C, Kuruvilla J, Xenocostas A, Stem Cell Transplant Steering Committee. Plerixafor for autologous hematopoietic stem cell mobilization and transplantation for patients in Ontario. Toronto (ON): Cancer Care Ontario (CCO); 2015 Sep 15. 45 p. (Evidence-based series; no. SCT-7). [33 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Sep 15

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario (CCO) supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Plerixafor Working Group

Composition of Group That Authored the Guideline

Working Group Members: C.T. Kouroukis, N.P. Varela, C. Bredeson, J. Kuruvilla, A. Xenocostas, Stem Cell Transplant Steering Committee

Financial Disclosures/Conflicts of Interest

Members of the Plerixafor Working Group and Their Conflict of Interest Declaration

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the authors of this recommendation report and internal reviewers were asked to disclose potential conflicts of interest. One author declared no conflicts of interest, and four (TK, CB, JK, AX) declared conflicts. TK reported receiving honoraria for work regarding plerixafor as a clinical reviewer for the Canadian Agency for Drugs and Technologies in Health. CB reported being the president-elect of the Canadian Blood and Marrow Transplant Group, which had received $5000 or more in a single year from Sanofi, the clinical developer of plerixafor. CB, JK, and AX declared that they had received research grant support from Sanofi. JK also declared that he had been a principal investigator for a clinical trial involving plerixafor.

The COIs declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by e-mail at ccopgi@mcmaster.ca.

Guideline Status

This is the current release of the guideline.

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Please visit the Cancer Care Ontario (CCO) Web site for details on any new evidence that has emerged and implications to the guidelines

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Cancer Care Ontario (CCO) Web site.

Availability of Companion Documents

The following are available:

- Plerixafor for autologous hematopoietic stem cell mobilization and transplantation for patients in Ontario. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2015 Sep 15. 6 p. Available from the Cancer Care Ontario (CCO) Web site.
- Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available from the CCO Web site.
- Program in Evidence-based Care methods handbook. Toronto (ON): Cancer Care Ontario (CCO); 2014 Sep 23. Available from the Program in Evidence-based Care (PEBC) Toolkit Web site.
- Program in Evidence-based Care document assessment and review protocol. Toronto (ON): Cancer Care Ontario (CCO); 2015 Apr 16. 15 p. Available from the CCO Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on January 4, 2016.

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